Personalized Tamoxifen: A Step Closer but Miles To Go

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Genetic variants in CYP2D6 lead to reduced conversion of tamoxifen to the active metabolite endoxifen. However, the role of the CYP2D6 genotype in predicting tamoxifen-associated outcomes remains controversial. Accurate assignment of the CYP2D6 genotype in archival tissues is crucial for future studies attempting to determine risk prediction of outcomes in tamoxifen-treated individuals. 

In this issue of Clinical Cancer Research, Schroth and colleagues (1) report that expanded coverage of CYP2D6 polymorphisms improves risk stratification and can be used as a predictor of outcome in tamoxifen-treated breast cancer patients.

Tamoxifen, the most common endocrine manipulation prescribed worldwide to treat individuals with estrogen receptor (ER)-positive breast cancer, significantly reduces both the risk of breast cancer recurrence and incidence of new disease (2). However, tamoxifen is not effective in all individuals. Tamoxifen is also frequently associated with bothersome side effects such as hot flashes, and, less commonly, with serious events such as venous thrombosis and uterine carcinoma. There is, therefore, great interest in using predictive biomarkers to personalize tamoxifen use.

Tamoxifen is metabolized extensively to active anti-estrogenic metabolites. In particular, the cytochrome P450 (CYP) 2D6 enzyme catalyzes the conversion of N-desmethyl tamoxifen to the active metabolite endoxifen (2). The enzymatic activity of CYP2D6 is highly variable due to genetic modifications, including single nucleotide polymorphisms (SNP), in the CYP2D6 gene. Dozens of CYP2D6 alleles have been described, and their prevalence varies among ethnic groups.

Initial investigations of the effect of CYP2D6 activity on tamoxifen metabolism focused on the CYP2D6*1 variant, the most common null allele in Caucasians. Plasma endoxifen concentrations were significantly lower among women with the CYP2D6*1 variant, compared with those homozygous to the wild-type allele, designated CYP2D6*1 (3). However, subsequent studies that correlated CYP2D6 polymorphisms with long-term outcomes in tamoxifen-treated women reported discrepant results (4, 5). Therefore, the clinical utility of CYP2D6 testing remains in question. Conceptually, the disparate results could be due to differences in study population, study design, persistence of drug therapy, missing data on concomitant CYP2D6 inhibitor use, and variability in methods to determine CYP2D6 genotype and metabolizer status (4, 5). The majority of published studies evaluated one or a handful of CYP2D6 polymorphisms using a variety of methodologies.

CYP2D6 polymorphisms can be detected by several high-throughput techniques. The AmpliChip CYP450 Affymetrix test, a microarray-based hybridization assay, was the first pharmacogenetic test cleared by the U.S. Food and Drug Administration for comprehensive analysis of the CYP2D6 genotype from genomic DNA extracted from whole blood. The matrix-assisted laser-desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS), which measures the molecular weight of the DNA bases by mass spectrometry, is frequently combined with allelic discrimination methods such as Thermus aquaticus polymerase (TaqMan), an enzyme-based assay, to detect known polymorphisms (6). Although these techniques detect SNPs in blood with high accuracy, the ability to genotype archival tissues has not been extensively investigated. One concern is that archival tumor tissue may provide low quality, fragmented DNA, leading to a limited utility of assays such as the AmpliChip CYP450 test. Tumor tissue is also associated with somatic changes and may not accurately reflect germ-line DNA. Nonetheless, genotyping of archival specimens is of practical importance because most previous clinical trials did not mandate a prospective collection of DNA, but frequently stored paraffin-embedded tissue. Several studies suggested that both MALDI-TOF and TaqMan can provide reliable and accurate determination of genetic polymorphisms in archival specimens (7, 8), and these methods were subsequently used in a number of the retrospective studies linking CYP2D6 genotypes and outcomes (4, 5).

In this issue of Clinical Cancer Research, Schroth and colleagues (1) compared the performance of CYP2D6 genotyping in paraffin-embedded tissues using the MALDI-TOF MS and TaqMan copy number assay (CNA) with CYP2D6 genotyping in DNA from stored blood specimens using the AmpliChip CYP450 test in 492 tamoxifen-treated individuals with breast cancer from a large German
cohort. The authors assigned a metabolizer phenotype using each of the tests, including extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM), defined as those with normal, reduced, and absent CYP2D6 activity, respectively, and correlated the phenotypes with breast cancer-related outcomes.

The study provides two important contributions to the literature. First, the authors report a very high concordance between the AmpliChip CYP450 test and MALDI-TOF MS CNA (99.2 to 100%, for the various CYP2D6 alleles that were tested). These results have important implications for future research. Although adjuvant clinical trials that both prospectively collect samples conducive for gene testing and determine outcomes in subjects with or without a variant are of most value, such trials require thousands of women, a decade or more from conception to results, and are costly. Alternatively, several large adjuvant trials have already been completed and provide both patient-related outcomes and archival samples. Therefore, methods that allow for multiple gene testing in archival specimens can be helpful to validate associations and to test new hypotheses.

Second, the authors report that the expansion of genotype analysis from testing the CYP2D6*4 allele to also include CYP2D6*3, *5, *6, and *7, increased the percentage of PMs from 5 to 8.3%. Moreover, the hazard ratio (HR) for disease recurrence in the PM group, relative to EM, increased from HR = 1.33 ($P = 0.58$), when only *4 was included, to HR = 2.87 ($P = 0.006$), when all five alleles were included. This finding is important as most previous studies tested only a handful of CYP2D6 alleles and, therefore, may have underestimated the proportion of PMs. These differences in CYP2D6 assessment could account for some of the heterogeneity seen in the literature, and highlight the importance of comprehensive assessment of CYP2D6 alleles.

So, where do we go from here? Although the authors suggest that comprehensive analysis of CYP2D6 alleles is important, the next question is are they all equally important, or do they all play an important role in tamoxifen...
metabolism? For example, CYP2D6*9, *10, and *41 alleles are associated with reduced enzymatic activity, whereas CYP2D6*3, *4, and *5 alleles are associated with no enzymatic activity (http://www.cypalleles.ki.se/cyp2d6.htm). In addition to variants in CYP2D6, polymorphisms in genes encoding for other enzymes involved in tamoxifen metabolism such as CYP3A5, SUIT1A1, or the target of tamoxifen and its active metabolites, the ER, can modulate tamoxifen response and should be considered (Fig. 1A; ref. 9).

In addition to host genetics, the use of concomitant medications can affect CYP2D6 activity. The authors do not provide information on concomitant use of CYP2D6 inhibitors, such as selective serotonin reuptake inhibitors, which are commonly coprescribed for treatment of coexisting depression or hot flashes. Borges and colleagues have recently proposed a CYP2D6-scoring system that can double the predictive ability of CYP2D6 phenotype by taking into account both the type of CYP2D6 genetic polymorphism and CYP2D6 inhibitor potency (10). Other environmental factors such as persistence with drug therapy, weight, and dietary factors could influence the effectiveness of tamoxifen in an individual patient (Fig. 1B).

Equally important, several tumor characteristics clearly influence tamoxifen response. Overexpression or amplification of human epidermal growth factor receptor 2 (HER-2), epigenetic silencing of ER, and gene ratio of homeobox 13 (HOXB13)/interleukin-17B receptor (IL17BR) are only a few examples implicated in tamoxifen resistance (Fig. 1C; ref. 11). Indeed, the authors have proposed composite indices comprising host and tumor factors, such as CYP2D6 polymorphisms and HOXB13 to IL17BR gene ratio (12). The concept can even be taken a step further, and a comprehensive index that incorporates a multigene assay of host- and tumor-associated factors, and possibly environmental factors, needs to be developed to truly individualize tamoxifen therapy.

In summary, although the study results move us a step closer to personalized tamoxifen, we are still miles away from fulfilling the promise. The phenotypic response of tamoxifen in an individual patient is unlikely to depend on a single polymorphism, but may be a result of the interplay of various host genetic factors, tumor biology, and environmental factors (Fig. 1). A comprehensive scoring system or an algorithm that considers all these factors has the potential to maximize the efficacy of tamoxifen while minimizing harms, and to successfully advance our journey toward “personalized tamoxifen.”

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